REMARKS

In the Office Action dated May 10, 2006, claims 1-29 were examined with the result that claims 12, 20 and 21 were allowed, while claims 1-11, 13-19 and 22-29 were rejected. The Examiner made the rejection final. In response, Applicant has filed a Request for Continuing Examination, the present Amendment wherein claims 30-35 have been canceled, and an exhibit attached to this Amendment comparing the biological activities of the presently claimed compounds of claims 13, 14, 15 and 16 with those disclosed in U.S. Patent 5,843,928, the primary reference utilized by the Examiner to reject the claims. Applicant is also enclosing a Glebocka et al article recently published in the Journal of Medical Chemistry, Vol. 49, pages 2909-2920 (2006) containing a discussion concerning the compounds of claims 13, 14, 15 and 16. In view of the enclosed exhibit, Glebocka et al article and the following remarks, reconsideration of this application is requested.

In the current Office Action, the Examiner rejected claims 1-11, 13-19 and 22-29 under the Doctrine of Obviousness Type Double Patenting as being unpatentable over claims 1-11 and 14-16 of U.S. Patent 5,843,928. The Examiner indicated that although the conflicting claims are not identical, they are not patentable distinct from each other since the presently claimed compounds are merely a selection of the compounds disclosed in the '928 patent, and are generically covered by the structure illustrated in the '928 patent. Although none of the presently claimed compounds are specifically exemplified in the '928 patent, the Examiner indicated that it would be obvious to one skilled in the art to prepare additional beneficial compounds because the '928 patent generically teaches such compounds for similar claimed uses.

In Applicant's previous response dated February 14, 2006, Applicant attempted to describe for the Examiner the differences in biological activities of the presently claimed compounds from those disclosed in the '928 patent. The Examiner, however, in the Office Action of May 10, 2006, indicated that although the data presented show the compounds of claims 13, 14, 15 and 16 have high intestinal calcium transport activity and

low or moderate bone calcium mobilization activity, it was "unclear what is high, low and moderate calcemic activity." Accordingly, in the present Office Action, the Examiner once again rejected the claims, and made the rejection final.

In response, Applicant submits the enclosed exhibit which consists of a table comparing the compounds of claims 13, 14, 15 and 16 with the closest prior art compounds of the '928 reference. The exhibit is believed to clearly illustrate the change of activity that occurs from untreated control upon administration of the compounds so that the Examiner can better understand the difference between "low," "moderate," and "high" activity. Applicant believes the enclosed table clearly illustrates the difference in the biological activities of the claimed vitamin D analogs versus the prior art compounds of the '928 patent.

THE BIOLOGICAL ACTIVITIES OF THE CLAIMED VITAMIN D ANALOGS

Applicant believes it would not have been obvious to select the presently claimed compounds from all of the compounds covered by the generic structure in the '928 patent because of the differences in the biological activities of the presently claimed compounds versus those described in the '928 patent. More specifically, the biological activities of the presently claimed compounds can be found in the specification in Figures 5 and 6 which are described in paragraph 00163 on page 58 of the specification as filed. As stated therein:

> "Figures 5 and 6 show a comparison of the calcemic activity of the known active 19-nor analog 2MD and the presently claimed F-Wit, 1AGR and 1AGS analogs. Figure 5 shows that F-Wit, 1AGR and 1AGS all have relatively high intestinal calcium transport activity, and are more active than 2MD in intestinal calcium transport activity. Also, Figure 6 shows that F-Wit, 1AGR and 1AGS all have significant ability to mobilize calcium from bone, and are less active in this regard than 2MD. Thus, in summary, the 2-propylidene-19-nor-analogs of structure I, and particularly F-Wit, 1AGR and 1AGS, show a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and moderate bone calcium mobilization activity."

Thus, the presently claimed 2-propylidene-19-nor-analogs in the present patent application all have intestinal calcium transport activity greater than 2MD (2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3). In addition, although the claimed 2-propylidene-19-nor-analogs have significant bone calcium mobilization activity, they are less active in this regard than 2MD.

Applicant believes the compound 2MD is the closest prior art compound disclosed in the '928 patent with regard to the presently claimed E and Z isomers of claims 15 and 16.

With regard to the E and Z isomers of compounds 13 and 14, Applicant believes the closest prior art compound is 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 which is also disclosed in the '928 patent.

THE BIOLOGICAL ACTIVITIES OF THE PRIOR ART VITAMIN D ANALOGS

The calcemic activities for the compounds 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 (referred to herein as 2MD) and 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 are set forth in U.S. Patent 5,843,928, particularly in Tables 1 and 2 found at columns 16 and 17 of the '928 patent. The '928 patent summarizes the calcemic activity of these two compounds beginning at column 15, line 61 and continuing through column 16, line 22 as follows:

> "Surprisingly, however, the 2-methylene substitutions produced highly selective analogs with their primary action on bone. When given for 7 days in a chronic mode, the most potent compound tested was the 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ (Table 1). When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the order of at least 10 and possible 100-1,000 times more than that of the native hormone. Under identical conditions, twice the dose of 1,25-$(OH)_2D_3$ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone. To show its selectivity, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-

> $(OH)_2D_3$ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day. The 2-methylene-19-nor-1,25-$(OH)_2D_3$ also had extremely strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. The bone calcium mobilization activity of this compound is likely to be 10-100 times that of 1,25-$(OH)_2D_3$. These results illustrate that the 2-methylene and the 20S-2-methylene derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from bone. Table 2 illustrates the response of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1."

Thus, it can be concluded from the above statement and the data contained in the '928 patent that the 2-methylene compounds have little, if any, intestinal calcium transport activity but have very potent bone calcium mobilization activity at the doses tested, as compared to 1α,25-dihydroxyvitamin D_3.

SUMMARY

Exhibit A is a chart which summarizes and compares the biological activities of the analogs 2MD and 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 as taught in the prior art '928 reference with the presently claimed hydroxypropylidene 19-nor-vitamin D compounds. Exhibit A illustrates the change of activity that occurs upon administration of 17, and/or 52 pmols of the two claimed E-isomer compounds versus the change of activity that occurs upon administration of 130 pmols of 2MD and 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3. With regard to the Z-isomers claimed, the chart of Exhibit A refers to pages 2913 and 2914 of the Glebocka et al article which states that the activities of these two compounds were less than the E-isomers. Unfortunately, however, the actual data was not reported for the Z-isomers.

A comparison of the 2-methylene analogs disclosed in the '928 patent and the hydroxypropylidene compounds of claims 13-16 in the present patent application shows that there are significant differences in the calcemic activities of these compounds. The 2-methylene analogs in the '928 patent have little, if any, intestinal calcium transport

activity and extremely high bone calcium mobilization activity. In contrast, the presently claimed hydroxypropylidene compounds of claims 13-16 all have relatively high intestinal calcium transport activity, "and are more active than 2MD in intestinal calcium transport activity" as stated in the present patent application (paragraph 00163 quoted above). In addition, the presently claimed hydroxypropylidene compounds, although having moderate ability to mobilize calcium from bone, "are less active in this regard than 2MD," as also stated in the present patent application (paragraph 00163 quoted above).

Thus, the presently claimed hydroxypropylidene compounds have significantly different calcium transport activity as well as bone calcium mobilization activity than the 2-methylene analogs disclosed in the '928 patent. Clearly, such activities would not be predicted based upon the structural similarity of the two compounds. One skilled in the art would have predicted that the compounds should have approximately the same intestinal calcium transport activity and bone calcium mobilization activity due to their structural similarity, but instead, it is clear that the presently claimed hydroxypropylidene compounds have much higher intestinal calcium transport activity and slightly less bone calcium mobilization activity than the 2-methylene analogs disclosed in the '928 patent. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs disclosed in the '928 patent.

Accordingly, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based on the 2-methylene analogs disclosed in the '928 patent.

In the Office Action, claims 1-11, 13-19 and 22-29 were also rejected under 35 USC §103(a) as being unpatentable over U.S. Patent 6,392,071 and 5,843,928. Again, the Examiner alleges that the hydroxypropylidene compounds claimed in the present application are obvious in view of the generic structure shown in the '071 and '928 patents and the fact that one of the substituents disclosed in the '071 patent is a hydroxyalkyl substituted on 2-methylene vitamin D compounds. Thus, the Examiner states that one skilled in the art would have been motivated to prepare additional compounds embraced

by the genus of the '071 and '928 patents as the presently claimed compounds are suggested by the references as a whole. Applicant, however, disagrees with the Examiner's conclusion for the following reasons.

The closest compounds taught in the '071 and '928 patents to the presently claimed hydroxypropylidene compounds of claims 13-14 is 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 and the closest compound taught in the '071 and '928 references with respect to the hydroxypropylidene compounds of claims 15 and 16 is 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 (the herein referred to 2MD compound).

Previously in these remarks, Applicant has distinguished the compounds of claims 13-16 from the 2-methylene compounds based upon their different biological activities (see Exhibit A and the arguments in the first half of these remarks). Thus, Applicant believes it has compared the biological activities of the closest compounds taught in the '071 and '928 patents with the claimed compounds of claims 13-16, and has indicated that such biological activities would not have been predicted based upon the structural similarity of the presently claimed compounds versus the 2-methylene compounds. The presently claimed compounds clearly have significantly different calcium transport and bone calcium mobilization activities than the 2-methylene analogs taught in the '071 and '928 references. As previously stated, one skilled in the art would have predicted that the compounds should have approximately the same intestinal calcium transport and bone calcium mobilization activities due to their structural similarities, but instead, it is clear that the presently claimed hydroxypropylidene compounds have much higher intestinal calcium transport activity than the 2-methylene analogs. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs, which are the closest compounds taught in the '071 and '928 references.

There are advantages to using compounds with high intestinal calcium transport activity versus compounds such as 2MD that have high bone calcium mobilization activity. For example, inflammatory bowel disease (IBD) is a disease of the intestine and

thus a compound having high intestinal activity, as opposed to bone activity, would appear desirable. Also, in patients with resectioned bowels, one desires to maximize activity in that patient's shorter intestinal route.

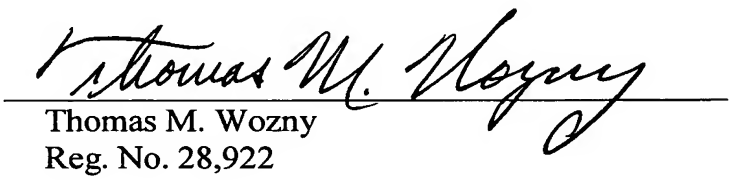
Thus, Applicant believes it has compared the biological activities of the presently claimed compounds to the closest and most structurally similar compounds disclosed in the '928 and '071 patents. As previously noted herein, the presently claimed hydroxypropylidene compounds have significantly different calcium transport and bone calcium mobilization activities than the 2-methylene analogs. Clearly, such activities would not have been predicted based upon the structural similarity of these compounds. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs taught in the '071 and '928 references.

Accordingly, Applicant believes the Examiner should withdraw the obviousness rejection based upon the '071 and '928 references.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

ANDRUS, SCEALES, STARKE & SAWALL, LLP

By 

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